Neurotoxicity, Neuroplasticity, and Magnetic Resonance Imaging Morphometry

What Is Happening in the Schizophrenic Brain?

Daniel R. Weinberger, MD; Robert K. McClure, MD

In an era of dramatic discoveries in neuroscience and genetics, it is likely that many popular theories and formulations about mental illness will need to be revised, if not discarded. The "neurodevelopmental hypothesis" is one of the popular theories about the origins of schizophrenia, which posits that abnormalities of early brain development increase risk for the subsequent emergence of the clinical syndrome.[1-3] An early piece of evidence in support of this hypothesis was the apparent lack of progression of cerebral ventricular enlargement observed with computed tomography during illness.[4-9] An important assumption of the neurodevelopmental hypothesis is that the putative primary pathologic condition of the brain is a reflection of abnormalities of early development. The neurodevelopmental hypothesis thus assumes that developmental neuropathologic conditions should arrest early in life and not continue to progress. The computed tomography results showing no apparent progression seemed consistent with this assumption. However, a recent series of magnetic resonance imaging (MRI) studies has called into question this assumption, by revealing changes in measurements of brain structures over short periods in patients who have been ill for varying durations and at various stages of life. These recent studies[10-14] have generated enthusiasm for a "neurodegenerative hypothesis," harkening back to proposals of Kraepelin and other neuropathologists during the first quarter of the 20th century that there is destruction of neural tissue associated with psychosis. In fact, results of MRI measurements have been cited as support for a much broader conceptual revolution in psychiatry, a "neurotoxicity hypothesis" for many psychiatric illnesses, including affective disorders[15,16] and anxiety and stress disorders[17-19] and even jet lag.[20] This recent trend has been bolstered by basic discoveries about the adaptability of neuronal connections[21] and the viability and reproducibility of neurons in the adult brain (eg, apoptosis and neurogenesis).[22,23] These developments have led some to opine that the neurodegenerative hypothesis of schizophrenia may have been unjustly overshadowed by the ascendancy of the neurodevelopmental hypothesis.[24]

While we are uncertain what constitutes appropriate relations between these 2 hypotheses, we are concerned that enthusiasm for the notion of neurodegeneration in schizophrenia (and in other psychiatric disorders) has outpaced the strength of the evidence. Quantitative measurements of cerebrospinal fluid spaces and tissue volumes on an MRI scan cannot establish that the brain has developed abnormally, nor can they establish that tissue has degenerated. If the principal evidence for abnormal brain development in schizophrenia rested on the interpretation of computed tomography or MRI volume measurements, this hypothesis would not deserve serious consideration. The evidence that abnormal brain development may be a risk factor for schizophrenia comes from several domains, including: (1) abnormalities of early motor and cognitive development and histories of

From the Clinical Brain Disorders Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Md.

Studies Showing Morphometric Changes

Investigators	Average Age of First Scan (years)	Average Length Follow Up (years)	Brain Region Showing Progressive Change	Maximum % Change (per Year)
DeLisi, et al, 1992, 1995, 1997, and 1998	26.4	1, 4, 4.7	Left Lateral Ventricle	(+) 3.0
			Left and Right Cerebral Hemispheres	(–) 1.42 (Right)
			Right Cerebellum	(–) 2.2
			Corpus Callosum (Isthmus)	(–) 1.14
Rapaport et al, 1997	14.8	2	Total Cerebrum	(–) 2.58
			Lateral Ventricles and VBR (Left>Right)	(+) 9.7
			Caudate	(–) 4.1
			Globus Pallidus	(–) 9.9
			Thalamic Area	(–) 7.1
Jacobsen et al, 1998	15.2	2	Total Cerebrum	(–) 2.30
			Right Temporal Lobe	(–) 4.15
			Superior Temporal Gyrus (Total)	(–) 3.7
			Superior Temporal Gyrus (Posterior)	(–) 4.3
			Right Superior Temporal Gyrus (Anterior)	(–) 3.2
			Left Hippocampus	(–) 7.15
Nair et al, 1997	31.3	2	Lateral Ventricle	(+) 12.48
Garver et al, 2000	35.8	2.6	None	
Gur et al, 1998	29.2	2.5	Frontal Lobe (Left>Right)	(–) 4.2 (Left)
			Temporal Lobe (Left>Right)	(–) 3.4 (Left)
Davis et al, 1998	39.5	5.1	VBR (Left>Right) in Kraeplinian patients	(+) 3.3
Lieberman et al, 2001	26	1.5	Cerebral cortex in poor outcome patients	(–) 0.42 (females)
			Total Ventricles in poor outcome patients	(–) 5.4 (females)
Mathalon et al, 2001	39.4	3.3	Prefrontal Sulci	(+) 6.63 (Left)
			Right Prefrontal Gray	(–) 2.12
			Right Frontal Sulci	(–) 2.71
			Left Frontal Gray	(–) 1.72
			Posterior Superior Temporal Sulci	(–) 9.65 (Left)
			Posterior Superior Temporal Gray	(+) 3.35 (Right)
			Left Lateral Ventricle	(+) 12.96

obstetrical adversity, (2) absence of evidence of neurodegeneration in postmortem tissue studies, and (3) association of developmental pathologic conditions with adult emergence of psychosis and related phenomena in animal and neurological models.[1-3] This represents a substantial body of research relating developmental compromise to subsequent schizophrenia and substantiating the neurobiological plausibility of this formulation. However, all of this evidence would be moot if neurodegeneration were apparent in postmortem studies. In contrast to predictions of a neurodegenerative hypothesis, the schizophrenic brain typically does not show loss of cortical neurons, gliosis, or any consistent evidence of degenerating or degenerated neurons.[25-27] It is often stated in the psychiatric literature that these negative findings are consistent with apoptosis.[13,14,24] The basis for this assertion is obscure, perhaps arising from research on apoptosis in early brain development or in non–central nervous system cancers (some of which are associated with cell death without inflammation) and from investigations of experimental excitotoxicity that were of short duration.[28]

Although apoptosis in early brain development does not typically initiate molecular activation of glia (although it may[29]), in most pathologic brain conditions associated with apoptosis—including epilepsy,[30] experimental excitotoxicity,[31,32] normal aging,[33] alcohol toxicity,[34,35] steroid toxicity,[36] Alzheimer disease,[37] and many others—astroglial activation is prominent.[28,30,38-42] Moreover, in conditions associated with loss of neurons and with apoptosis, the neurons and glia that survive and those that are dying increase expression of genes and proteins that are aimed at molecular compensation and restoration or are involved in cell suicide.[43,44] These changes are characteristically not seen in brain tissue of patients with schizophrenia.[43,45] Much has been made of the lack of gliosis in the schizophrenic brain as failing to support neurodegenerative hypotheses, but it is the lack of expression of genes involved in cellular responses to injury and to DNA fragmentation that most militates against neurotoxicity and neuronal destruction hypotheses. Furthermore, the sine qua non of apoptosis is cell death, and diminished populations of cortical neurons are generally not found in tissue, including that of older patients who have

Brain Region Showing No Change or Opposite Change	Correlation with Clinical Change
Right and Left Temporal Lobes Right and Left Superior Temporal Gyri Right and Left Hippocampus/Amygdala Right and Left Caudate	No significant correlation between clinical measures and changes in ventricle or cerebral hemisphere volume; overall, symptoms improved in patients
None	Overall, symptoms improved in patients
Left Temporal Lobe Left Superior Temporal Gyrus (Anterior) Left and Right Amygdala Right Hippocampus	No significant correlation between temporal lobe volume decrease and hallucinations, delusions, or negative symptoms; overall, symptoms improved in patients
None	Not reported
Lateral ventricle Total Brain	Worsening of symptoms correlated with decreased ventricular and increased total brain volume
Whole Brain Cerebral Spinal Fluid Spaces	Improvement in most symptoms correlated with decreased frontal and temporal lobe volumes in previously treated patients; overall, symptoms improved in patients
None	No significant correlation between change in ventricle-to-brain ratio and negative symptoms in non-Kraeplinian patients
Caudate Nuclei in all patients Hippocampus in all patients Cerebral Cortex in all patients Total Ventricles in all patients Total Ventricles in good outcome patients Cerebral Cortex in good outcome patients Hippocampus in poor outcome patients	Total ventricle and cerebral cortex increase correlated with poor outcome; cerebral cortex and hippocampus increase correlated with good outcome
Left Prefrontal Gray Left Frontal Sulci Right Frontal Gray Anterior Superior Temporal Sulci Right Anterior Superior Temporal Gray	Overall, symptoms improved in patients

suffered psychotic symptoms all of their adult lives.[25-27,46] Therefore, although the lack, to date, of neurodegenerative signs in postmortem tissue does not rule out tissue damage, it raises the bar for believing other evidence that neurodegeneration has taken place. At some point in the disquisition, for neurodegeneration to be a plausible scenario, sequelae of neurodegeneration must be observable at the tissue level.

The evidence said to support the notion of neurodegeneration, although not present at the tissue level, is based on 2 phenomena. First is the apparent progression of clinical aspects of the syndrome in some patients, such as personality deterioration, dilapidation, and treatment resistance.[13] Curiously, in longitudinal studies of cognitive function (a potentially direct measure of the integrity of cortical neuronal systems), most of the data do not support progression, at least during about the first 20 years of illness (reviewed in Rund[47]). Many unfortunate human circumstances and behaviors appear to get worse over time in some individuals (eg, joblessness and homelessness), without necessarily implicating degeneration of brain tissue. Although unemployment for a long period may in fact be associated with dynamic changes in synaptic architecture—just as learning new behaviors and habits may involve changes in the connections made between cells—these presumably are plastic modifications (ie, potentially reversible), not toxic degenerations (which usually imply irreversibility).

The second line of evidence for neurodegeneration is progressive changes in volume measurements in structural MRI studies. This literature is selectively abstracted in the **Table**. Although there are some studies[24,48-56,58] that find evidence of changes in MRI volume measurements, the results vary considerably among these positive studies. Some changes, eg, in temporal lobes, frontal lobes, and cerebrospinal fluid spaces, have been found in more than 1 study. However, no 2 studies have found the same pattern of changes across all of these measures, and each study appears to have its own unique combination of results. Moreover, although correlations between changes in symptoms and in measurements have been reported in a few studies,[51,52,54,55] these also vary, and, remarkably, in most studies, patients have improved symptomatically while their MRI changes have ap-

peared to progress. This is hardly what would be predicted as a result of progressive loss of brain tissue; it is difficult to conceive of neurodegeneration being associated with clinical improvement.

Further concerns about inferring neurodegeneration in schizophrenia from MRI volume measurements are raised by comparisons with neurological conditions in which neurodegeneration is established. The magnitude of the changes reported in the studies purporting to show neurodegeneration in schizophrenia is not trivial. For example, Mathalon et al[24] claim a 2% per year reduction in frontal gray matter in patients with schizophrenia who have been ill for a mean of 15 years before they were studied. This degree of change is near the range reported in Alzheimer disease for the hippocampus, a structure that is markedly degenerated in this illness.[59] Other investigations of schizophrenia have reported volume loss in the hippocampus of greater magnitude, as much as 7% per year,[54] yet postmortem studies of schizophrenia have had difficulty uncovering evidence of even slight hippocampal shrinkage.[27,43] The mesial area of the thalamus was shrinking at the rate of 7% per year in a study[52] of adolescent patients with already chronic disease. Presumably, the tissue loss would have to spontaneously arrest fairly soon, or these patients would be virtually thalamusless by middle age. In a recent study[24] of patients in their fifth decade of life, the left lateral ventricles were increasing at a rate of 13% per year, thus doubling in size every 8 years, again at a rate that is seen in Alzheimer disease.[60] In the study[52] of adolescent patients who had been ill for several years, the rate of ventricular volume change was 10% per year, translating into a doubling period of 10 years. At this pace, by the time a patient with schizophrenia reached age 60 years, there would be little brain left. Although it has been countered that the progressive MRI changes in schizophrenia may not be linear and may not occur throughout the course of illness,[11,52,54] similar progressive changes that have been reported in adolescent patients with several years of disease,[52,60] first-episode patients in their 20s,[55] patients in their 40s,[24] and patients in their 50s[56] make this counterargument unconvincing (unless one concludes that the neurodegeneration only occurs during the few years when patients are part of a National Institute of Mental Health–funded study). It is hard to imagine how the magnitude and duration of changes observed in MRI studies of patients with schizophrenia could be occurring as a neurodegenerative process, whether by cell necrosis or apoptosis, without observable evidence of neuronal loss and other related changes in postmortem tissue.

If the MRI changes, which are found at least in some studies, do not reflect neurodegeneration, how might they be explained? Variations in MRI measurements can reflect differences in image acquisition and analysis techniques, alterations in neuronal and nonneuronal tissue compartments, physiological alterations in brain tissue (eg, changes in tissue perfusion, fat, and water content), and changes in other chemical constituents that make up living brain.[61] Indeed, numerous studies have shown that changes in body weight,[62] alcohol intake,[63,64] steroid administration,[65] and hormonal status[66] can rapidly produce changes in MRI volume measurements, some of greater magnitude than those reported in the schizophrenia studies. Recent findings that ventricular size can alternatively increase, decrease, and then increase again in the same patients scanned repeatedly over a few months suggest that such changes may reflect physiological variations.[51,57] A recent report[67] claimed that only 4 weeks of treatment with lithium carbonate increases cortical gray matter volume by 3%. Treatment with paroxetine hydrochloride was reported to decrease thalamic volume by 19% in 12 weeks.[68] Neuroleptics also may rapidly change brain volume,[69] perhaps because of changes in tissue perfusion, and many studies[70,71] have shown a relationship between neuroleptic exposure and basal ganglia volume change.

It is also conceivable that, in addition to physiological variations, the MRI changes reflect some degree of neuroplastic adaptations to the environment or to the experience of being psychotic, perhaps reflected in less abundant neuropil, as has been observed in postmortem tissue from patients with schizophrenia.[26] Indeed, investigations of gene and protein expression in schizophrenia suggest that there is decreased transcriptional drive related to various signal-processing pathways.[43] This may reflect environmental factors reducing the neuronal information-processing load. These factors may include unstimulating environments, the effect of long-standing diagnosis of a chronic disease, comorbid conditions (including smoking, alcohol or other drug use, and untreated medical problems), and effects of long-term medication use. It has become clear from studies in experimental animals that numerous environmental factors have an effect on neuronal plasticity and can be associated with regression of dendrites and spines, possibly reflecting reduced stimulus-linked gene expression. It is also conceivable that a brain that processes information abnormally, perhaps because of genetic and developmental aberrations that may be factors in schizophrenia, would make unique plastic adaptations to environmental experience. These nondegenerative adaptations, however, are potentially reversible (as part of how a brain does business with environmental stimuli), in contrast to the implications of changes that reflect neurodegeneration. Although the possibility of such plastic alterations in neuronal connectivity is intriguing, it is not clear that their magnitude would be observable at the level of an MRI measurement. In the often cited study[72] of stress-associated cellular changes in the monkey hippocampus (one of the reports that launched the experiential neurotoxicity revolution), although dramatic cytoarchitectural changes were described, including loss of neurons and gliosis, there was no change in gross hippocampal volume! Moreover, in studies[73-75] of patients with epilepsy, seizure frequency, a plausible measure of neurotoxicity load, tends not to correlate with hippocampal volume reductions seen on MRI.

Based on these various considerations, we caution investigators involved in MRI studies and readers of this literature to suspect the improbability of the reported volume changes as being related to neurodegenera-

tion. In our view, the implications for patients and families of such an extreme interpretation of the data require more definitive evidence, which cannot emerge from such MRI measurements.

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Corresponding author and reprints: Daniel R. Weinberger, MD, Clinical Brain Disorders Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, 10 Center Dr, Bldg 10, Room 3C-101, MSc 1255, Bethesda, MD 20892 (e-mail: weinberd@dirpc.nimh.nih.gov).

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